Clinical Proceedings

of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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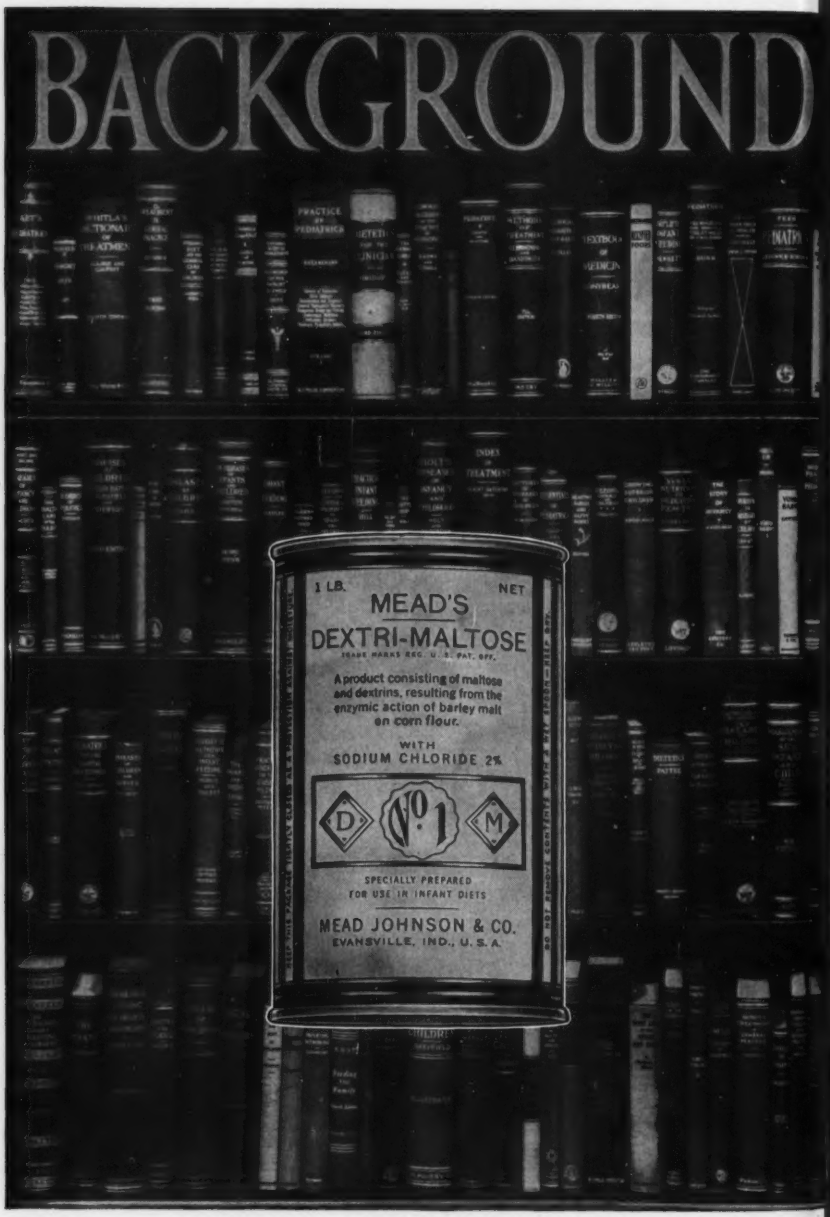

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SYMPOSIUM ON WILMS' TUMORS*

William F. Burdick, M.D.
W. Dabney Jarman, M.D.
D. Joseph Judge, M.D.
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Warren Sager, M.D.

Dr. Judge:

Tumors of children, although observed infrequently in general practice or general hospital practice, are a problem of importance to a children's hospital. Cancer places very high among the causes of childhood mortality. In the past many tumors of children of the one to four age group have had a higher mortality than others. This probably is attributed to the fact that after the infant stage the child is rarely taken to a physician routinely until it begins school. One tumor occurring in this age group is Wilms' tumor. All of the published reports concerning this tumor give a poor or nearly hopeless prognosis. An attempt will be made in this discussion to review the clinical, surgical, urological, roentgenological and pathological aspects of the tumor, and with a review of the cases at this hospital from the period of 1934 until 1948, to realize information that will improve our knowledge and our statistics.

Dr. Burdick:

The pediatrician is usually the first one to see these cases so it is appropiate, in a symposium such as this, to call his attention to some of the clinical features of the disease. There are several tumors in the kidney area indistinguishable except by histological examination after surgical removal. There is the neuroblastoma of the adrenal tissue, the unattached retroperitoneal embryonal tumor and the embryoma of the kidney, or Wilms' tumor. It is important, moreover, to know before operation just which type of tumor we are dealing with.

All of the tumors in this group are malignant and are usually well encapsulated. They remain small for an unpredictable period of time, then enlarge suddenly and rapidly. The sudden enlargement is caused by massive hemorrhage which occurs into the rapidly growing tumor. Several days after a complete physical examination when no mass is felt the child will present a very large abdominal tumor. On this basis we can

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rise to the defense of the pediatrician who often has seen the child a few weeks before the tumor mass is discovered by someone else.

So far as symptoms are concerned they are conspicuous by their absence. These children do not present the urinary tract symptoms found in adults. The first thing that is noted is a palpable abdominal mass. This is often noticed by the parent before it is felt by the physician. The mass is solid, non-tender and not mobile. The border is usually smooth and rounded sometimes extending to the midline and down into the iliac fossa. Since early diagnosis and the treatment are imperative, all of us should palpate every child's abdomen thoroughly and deeply in our routine physical examinations.

The differential diagnosis may present some difficulty at times. The twelve year old colored boy included in our series, and who was seen here in March 1948, had an admitting diagnosis and clear clinical picture of appendicitis. These masses may be confused with enlarged livers, cysts of the liver and enlarged spleens. The latter masses lie directly beneath the abdominal wall and splenic notch can often be palpated in the splenic tumors. Tumors in the kidney area lie deeper and tympanic bowel frequently overlies them.

The intravenous pyelogram has its greatest value in establishing the presence of the other kidney. The calices can be distorted from a lesion in the kidney or a large surrounding mass pressing on the kidney.

We all hope now, though the efforts of the Tumor Board, and the interest in these cases at Children's Hospital, to have better results in the future with our patients suffering from Wilms' tumor.

Dr. Jarman:

The record of Wilms' tumors seen and treated here at Children's Hospital is one not to be envied. The record from other hospitals seems considerably better, and therefore puts us in a bad light as far as other statistics are concerned. It should behoove us to find out if possible why others are getting better results than we are. I thought it might be revealing to give you some of the statistics of other men. So far as statistics are concerned, they bear out what I have just said—that ours are much worse.

The best results thus far reported are those of Silvers[1] from the University of California. In his series of 18 patients with Wilms' tumor, thirteen had nephrectomy and ten were alive from 2 to 15 years following treatment, a survival rate of 76.9 per cent. He emphasized that there was no standard treatment used. Every patient who survived had had a nephrectomy. Three of the four patients who had nephrectomy without either pre- or post-operative irradiation were alive and well from nine to fifteen years. Pre-operative irradiation was used only if technical removal,

because of the tumor's size, was impossible. The majority of the patients in his series had the kidney removed through a postero-lumbar incision. Interestingly, one of his patients developed pulmonary metastasis seven months following nephrectomy, and following x-ray therapy alone for this metastasis, the child is well two years without recurrence. Truly, this is an amazing survival rate. No details were given with reference to the type of post-operative irradiation, and therefore I cannot comment on this.

Weisel et al[2] and Priestley and Schulte[3] from the Mayo Clinic have published articles on Wilms' tumors but several of their patients were adults and the figures are not suitable for our discussion in children today. Neumyer[4] reported seven cases all of whom died within five months following operation. Nesbitt and Adams[5] have an interesting series and I would like to go into this a little bit more in detail. They had a total of 16 cases, with eight alive from three and one-half to four and one-half years following operation. One case was considered inoperable from the size of the tumor, as well as the presence of pulmonary metastasis. However, a punch biopsy was done and was adequate for a positive diagnosis of adenomyosarcoma. The patient was given x-ray treatment only and is alive and well ten years following the diagnosis. Two patients had at the time of nephrectomy evidence of retroperitoneal extension of the tumor, and I believe are well following post-operative irradiation. In comparing these figures with ours, what we have been doing needs improvement.

The question of the surgical approach has come up from time to time, and I think a word should be said regarding this. Statistics do not prove that the transverse approach gives a better prognosis than a postero-lumbar approach. However, I do feel that if there is anything to getting at the renal pedicle first, then the transperitoneal approach should be used. Recently, Sweetser[6] has advocated an incision which does away with going through the peritoneum. This is an incision which begins as a loin incision and is carried down across the right rectus muscle and then up the midline to the zyphoid. Turning this flap back and pushing the peritoneum medially enables one to get at the pedicle first.

When these renal tumors come within the province of the genito-urinary specialty, the urologist must make every effort, which I feel he has done, to try to salvage some of these tragic cases. At the present time, it is my feeling that nephrectomy should be done as soon as the diagnosis is made, if it is technically feasible. If the tumor is too large, pre-operative irradiation should be used, and just as soon as the tumor is operable, remove it, rather than wait the conventional 4–6 weeks. To my mind, the most important adjunct in the treatment of these tumors is radiation.

This should be given in as large doses as can be tolerated, and I feel should be given to the entire lymph drainage area where metastases are likely to occur. This means the mediastinum and the nodes on both sides of the aorta. Should a local metastasis arise, I do not feel that surgery is out of order. As far as the type of approach is concerned, I feel that everyone would be willing to use the same approach, whether it be transperitoneal or retroperitoneal, in an effort to get a uniform followup series. The recently established Tumor Board seems to me a good medium through which to work.

The prognosis for children with malignancies of the kidney, I definitely feel, will depend upon three factors: as early diagnosis as possible; nephrectomy as soon as possible; and intensive, complete postoperative irradiation.

Dr. Sager:

Wilms' tumors occur so infrequently in an individual surgeon's practice that it is necessary for purposes of study to rely upon the results obtained in their treatment by many individuals and on those of institutions where there is a great concentration of pediatric material. It is hoped that one result of the organization of a tumor board in this institution will be a more complete record of these cases and that a study of the methods used in treatment will lead to rapid accurate diagnosis and a determination of the best plan of therapy.

The use of x-ray therapy in the treatment of Wilms' tumors is an important addition to surgical removal. Pre-operatively it does not destroy all the malignant cells but it does decrease the size of the tumor making surgical removal less difficult. To accomplish these results a period of from two to three weeks of treatment is required. Because of this delay Ladd and White[7], and Ladd and Gross[8] do not advocate its use. Any decrease in their mortality rate, which is one of the best, they feel is more than balanced by the danger of metastatic lesions developing during the period required to obtain results from x-ray treatment. Post-operatively x-ray therapy is generally used. The degree of its effectiveness may be questioned but it can do no harm and there is always the possibility of a cure or a prolongation of life resulting from its use.

Transfusions should be given before operation if indicated. Preparations for blood and fluids should be made in order to combat the effects of shock, if it occurs. X-ray examination for the purpose of discovering metastastic lesion should be done before operation. Surgical removal of the tumor should be carried out as soon as the necessary information as to the child's condition can be obtained and necessary corrective measures completed.

The types of approach to the tumor in general use are through an oblique postero-lateral incision in the flank, or anteriorly through the anterior

abdominal wall. The anterior abdominal wall incision may be made from the costal margin downward either retracting the rectus muscle laterally or splitting its fibers. A transverse incision has been used by some operators. The anterior approach allows for the removal of the tumor with less handling before the renal pedicle is reached and also makes possible adequate exposure for large tumors which may be difficult to obtain through an oblique postero-lateral incision. For the reasons mentioned the anterior incision is probably the one of choice.

Dr. Lattman:

A definite diagnosis of Wilms' tumor cannot be made from the roentgen findings alone. A plain film of the urinary tract may reveal the intestines to be displaced toward the opposite side by a smooth round mass of increased density; the psoas shadow on the affected side not visualized at all or not as clearly visualized as on the normal side; occasionally some calcific shadows may be visualized on the affected side. The above findings, however, occur only when the tumor is large enough and old enough to show calcific changes. In many cases where the tumor is small and young the plain film is negative. In urograms, preferably intravenous, as in the plain film, results may be negative if the tumor is small and does not impinge on the pelvis of the kidney. If the tumor impinges on the kidney pelvis, distortion, fragmentation and distention of the pelvis and calices may occur in different cases.

It is difficult, if not impossible, to make a differential diagnosis by roentgenological means alone between a neuroblastoma which often occurs in this region, and Wilms' tumor. Occasionally the pelvis of the kidney, in the case of a Wilms' tumor, may be so elongated and so stretched and a smooth arc described, as to suggest a polycystic kidney. Polycystic kidneys are usually bilateral, but even then a conclusive differential diagnosis cannot be made. A complete urological workup must include x-ray studies of the chest, long bones and skull, because the difference of location of metastatic foci are of help in making a differential diagnosis. The neuroblastoma usually metastasizes to the lungs, pleura and liver.

In tumors of the kidney the radiologist is of greater help in the realm of therapy than he is in the realm of diagnosis. As to x-ray therapy, there are several schools of thought including those who advocate pre- and post-operative, post-operative alone and no therapy at all. All agree that surgery is essential and that if the tumor is too large for removal for technical reasons, pre-operative therapy must be used in order to make the tumor removable.

The statistics of the different groups are not large enough nor sufficiently convincing, to me at any rate, that any one group has the final truth. The

record of our own hospital in the Wilms' tumors is sad indeed, no matter how the patient is treated, and we have treated them in the different ways mentioned above. The records of other hospitals are good but there seems to be no absolute uniformity of treatment. Each case must be considered separately and treated accordingly. Only a few years ago Ladd and Gross advocated neither pre- or post-operative radiation, although they had to resort to pre-operative when the tumor was too large for removal. In the last few years, however, they have become staunch advocates of post-operative therapy to be used immediately following the nephrectomy.

As a radiologist I am firmly convinced that a short but intense course of pre-operative therapy which can be given in two weeks, should be used in most cases. In addition to shrinking the tumor and making it an easier procedure, the lymphatics in the surrounding areas where metastatic cells may be present are treated and destroyed. The rate with which the tumor decreased in size is a help in the differential diagnosis between Wilms' tumor and neuroblastoma, as Wilms' tumor decreases in size with small doses of x-ray much more rapidly than does the neuroblastoma. This is to be followed by a more intensive course of x-ray therapy, immediately following nephrectomy.

It is to be hoped that with a tumor board now established in this hospital a more thorough study of each case will be made. Better records will be kept and some way of getting the patient to the clinic earlier will be devised. This will lead us to more rapid and accurate diagnosis and to a more definite plan of therapy.

Dr. Rice:

In considering the abdominal tumors which one is likely to encounter in a child five years of age or younger, we will not encounter too much difficulty in making a fairly accurate diagnosis if the cystic tumors and hepatic tumors are eliminated. High on the list of probabilities will come the neuroblastoma and embryonic tumors of the kidney (Wilms' tumor).

Both of these tumors are fairly well fixed and in general are found on one side of the abdomen. The lack of nodularity tends to distinguish the adenomyosarcoma (Wilms' tumor) from the neuroblastoma. While both may be associated with the kidney, either by invasion or by arising from it, the neuroblastoma may have its origin quite apart from the kidney and may not involve it in any way. The tumors are quite different in the matter of their metastases, the neuroblastoma tending to much more extensive metastases and at greater distances from the original site. Both invade the lung and the liver, but Wilms' tumor rarely extends beyond these organs and the structures in the abdomen, whereas neuroblastoma may show extensive involvement of bones, and tumor bearing areas in the skin, the orbits and brain.

Structurally Wilms' tumor is usually rounded or slightly elongated. Though it may be firm, it is not uncommon to find areas of degeneration and hemorrhage intermixed with firm portions which may be representative of connective tissue, cartilage, or bone. As a part of the tumor mass will be found the remains of the kidney either extending from it or enveloped by the tumor. The adjacent lymph nodes, liver and lungs are commonly involved.

Microscopically the tumor is made up largely of epithelial masses in some areas of which can be noted tubular like structures. Connective tissue is also usually prominent and muscle fibers and occasionally cartilage and bone are sometimes seen. Blood vessels not infrequently contain tumor cells.

It is difficult to understand how some of these tumors can reach the size of a small football without being noticed by a parent. However the statement that one of these children was examined by a competent urologist, who found no abdominal tumor just three weeks before a sizable mass was recognized here, gives us some idea of the speed with which they can enlarge. This is a good argument for their prompt removal and perhaps this child's being alive today may be due to the promptness with which he was operated on.

The poor results obtained and the diversity of approach and treatment make the study of this type of malignancy by the Tumor Board a logical one. Through the united interest of those who are concerned with the subject, viz. pediatricians, surgeons, radiologists and pathologists our knowledge will increase and our results are bound to be better.

Dr. Judge:

A review of our statistics since 1934 reveals that there have been a total of 24 cases.*[9] Thirteen were males, 11 females, while 14 were of the white race and 10 colored. The tumor was on the left side in 14 cases and on the right in 10. No incident of bilateral tumor was noted, a situation reported by others. Table I tabulates the patients according to age and it is seen that 17 cases or 70.8 per cent were in the age group from one to five years.

In the majority of cases of Wilms' tumor the first symptom is painless progressive enlargement of the abdomen with the discovery by the parent of an abnormal mass in the abdomen. Table II enumerates the symptoms of our patients. If the child is seen early it will be well nourished and well developed, while weakness, vomiting and abdominal pain occur in those

* Cases included in this review include 19 cases of Wilms' tumor at the Children's Hospital reviewed by Drs. Lois Murphy and F. Leyva in May 1946. (To be published.)

patients seen in the later stages of the disease. Hematuria occurred in only four cases or 17 per cent and was usually noted late in the course of the disease.

Because the number of patients is limited and the treatment varies considerably, it has been difficult to come to any definite conclusions. Since 1936 the tendency in treatment here has leaned slowly toward that of Priestly and Broders[10] although as of this date from the apparent success of Ladd's group in Boston, the latter opinion seems to offer the best results and consequently the preferred course of treatment. Prior to 1946 of the

TABLE I

AGE	CASES	PER CENT
5–12 mos.	3	12.5
1–2 yrs.	4	16.7
2–3 yrs.	10	41.7
4–5 yrs.	3	12.5
5–6 yrs.	2	8.3
6–7 yrs.	1	4.1
12 yrs.	1	4.1

TABLE II

Symptomatology

	CASES
Abdominal distention or palpable mass	16
Abdominal pain	7
Vomiting	5
Hematuria	4
Fever	2
Urinary frequency	2
Weakness	1

19 cases seen 14 were proven microscopically and had operative intervention. Three patients had x-ray alone when the condition of the patient was extreme, while 2 patients were seen terminally and received no treatment. Six children received pre-operative radiation and 13 cases, all but one of the 14 operated upon, received post-operative radiation.

As has been stated, with the advent of increased knowledge and organization of treatment of tumor cases since 1946, policy has changed. As yet because of the small number of patients and the insignificant time interval no conclusions can be drawn. Of the five children treated in the later period, all were operated upon and four are alive to date. One patient

who had an immense infiltrating, necrotic tumor died during operation. One of the 4 living children received pre-operative radiation because of the size of the mass. Significantly enough, this child had been seen prior to admission because of abdominal distention two months previously. All the remaining patients received post-operative radiation. One child has a recurrence of the tumor mass in nine months. The other two are symptomless and without clinical signs after six months.

The technique of operation for the five cases in the new group was the abdominal approach in two and the oblique flank incision in three. Silvers[4] has reported 77 per cent cure with the nephrectomy incision but review of the combined statistics of others seems to favor the abdominal approach.

Although the value of post-operative radiation cannot be denied, it is interesting that in the one cure from this hospital neither pre- or post-operative radiation was given. This child of 17 months was first seen with the presenting complaints of abdominal distention and is now well, 45 months post-operatively. The infant, interestingly enough, had had a complete urological workup at a large institution three weeks prior to admission, there being no evidence of the tumor at that time. This can be explained easily by the rapidly growing nature of the tumor or the fact that often there is no disturbance in the intravenous pyelogram. This case might well emphasize the danger of postponement of operation for any length of time.

The variance of survival rate from 77 per cent in one section of the country to zero in another certainly does not depend solely on the malignancy of the tumor although Silvers possibly may have a group of patients with tumors of low malignancy. There are several points which seem to be most important. One, the education of the physicians and teachers as well as parents to the existence of Wilms' tumors and tumors of children in general. Two, consideration of abdominal tumors as a strict emergency in children. Three, restriction of examination and palpation of the abdomen to an absolute minimum. Four, standardization of all procedures, as far as possible, with the use of the best operative technique along with adequate post-operative radiation. These objectives along with the formation and operation of a tumor board to insure the unanimity of techniques and adequate follow-up, will help to better the situation concerning Wilms' tumor.

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EARLY ORAL FEEDING IN THE TREATMENT OF INFANTILE DIARRHEA

Case Report No. 137

Robert O. Warthen, M.D.

The following cases are reported as examples of the use of full-strength formula feeding in infants with diarrhea rather than the conventional practice of early starvation followed by a gradual increase in oral feedings as dictated by the character of the stools.

As originally stated by Park[1] and more recently reiterated by Chung[2], the clinical state of the infant rather than the character of the stools should determine the course of treatment prescribed for any given case of diarrhea. The cases herein conform to the report of Chung and Viscorova[3] in which good clinical results were achieved on full formula feedings of infants with diarrhea.

Chung demonstrated that the absorption of food improved on full-strength formula intakes as compared with conventional reduced food intakes, even though a larger volume of food was excreted. Hence, since more food is absorbed, it would appear desirable *not* to restrict the food intake in infantile diarrhea.

Chung and Viscorova[3] also showed that the duration of diarrhea was not prolonged under a full feeding regime; moreover, a more prompt and constant weight gain was observed in those fed full-strength formulas.

Case #1: W. D. 48–10099

W. D., a 3½ week old, 5 pound 4 ounce colored female, was admitted to this hospital after having passed approximately 30 watery green mucous stools during the preceding 48 hours. She was the product of a seven month uncomplicated pregnancy and weighed 5 pounds 12 ounces at birth. There were no neonatal complications. With the exception of having been breast fed during the first week of life, her formula had consisted of 4½ ounces of evaporated milk, 9 ounces of boiled water and 2 tablespoons of Karo. Adequate vitamin supplements had been supplied. She had been unable to retain more than one ounce of this mixture at any one feeding, and an inadequate weight gain had been observed during the neonatal period. The family history was non-contributory.

Frequent vomiting spells marked the first 24 hours of the present illness; however, during the 24 hours prior to admission she retained small amounts of tea and milk. No fever was noted.

Upon admission her temperature was 99°, pulse 140 per minute and respi-

rations 20 per minute. Physical examination was essentially negative with the exception of marked malnutrition and slight dehydration. A hemogram and urinalysis were within normal limits.

Therapy in the hospital consisted of a full-strength Olac milk formula, 5% glucose water orally between feedings and daily prophylactic procaine penicillin. Fifty calories per pound of body weight of formula were taken

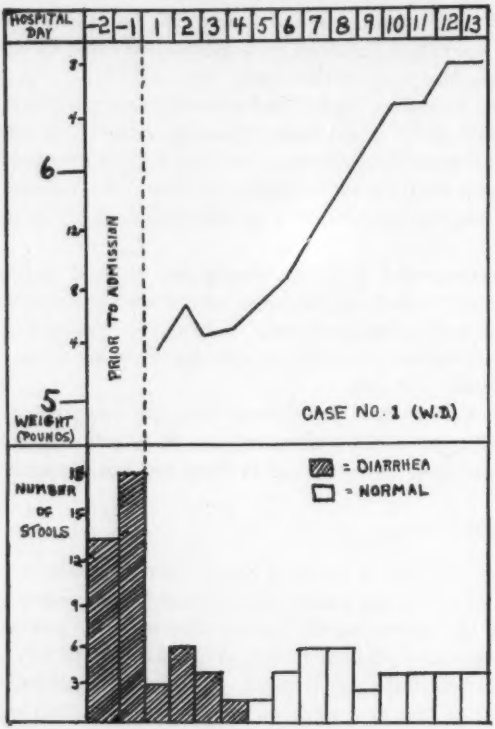

CHART 1

during the first hospital day, this being increased as tolerated to 80–92 calories per pound per day.

The diarrhea persisted for the first four hospital days. However, the stools subsequently achieved a better consistency and the infant began to pass from one to six normal stools per day. Daily weight gains have been constant and at the present time (13th hospital day) she weighs 6 pounds 8 ounces; at no time has her weight been below that on admission (Chart 1).

Case # 2: G. S. 48–10680

G. S., a three month old white female, was admitted with the history of having had 10 watery green stools during the preceding 48 hours. For a week prior to admission she was reported to have a "running nose" with an occasional "coughing and choking spell." The infant had refused most of her formula for the three days prior to hospitalization and vomiting had

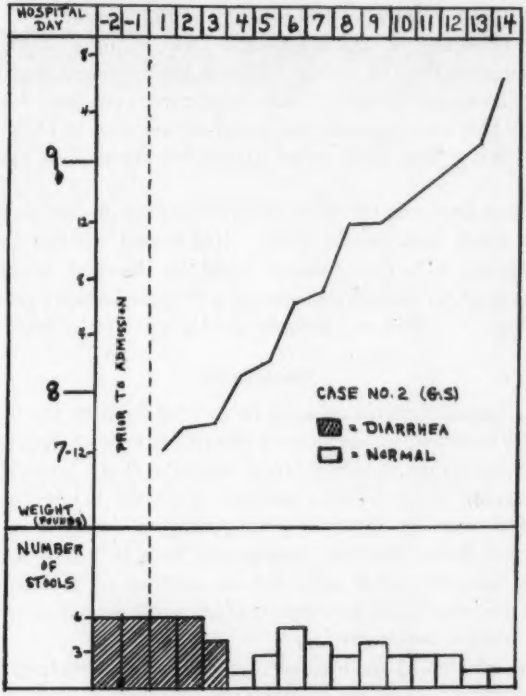

CHART 2

occurred once during the day of admission. There had been no previous bouts of diarrhea.

Her birth weight was 6 pounds and she was the product of a full term, uncomplicated pregnancy. The delivery was uneventful and there were no neonatal complications. The patient had been bottle fed during the first two months of life on a formula consisting of varied dilutions of evaporated milk, boiled water and dextrimaltose with resultant projectile vomiting of two-thirds of the feedings. At 2 months of age the evaporated milk

was replaced by full strength Olac (23 calories per ounce) with a prompt cessation of vomiting.

The family history was irrelevant.

Physical examination upon admission disclosed an athreptic, slightly dehydrated female infant with a mild rhinitis and pharyngitis. The remainder of the examination was essentially negative. A hemogram revealed a hemoglobin of 10.5 gms. but was otherwise normal. Urinalysis was negative and an x-ray of the chest was within normal limits.

Therapy consisted of a full-strength Olac formula supplemented by mashed bananas as desired. Penicillin was administered prophylactically. Sixty-five calories per pound of body weight were retained during the first 24 hours and this was gradually increased as tolerated to 75–85 calories per pound per day. Four days after admission cereal and egg yolk were begun.

The diarrhea persisted for the first three hospital days after which one to five normal stools were passed daily. Her weight steadily increased and when transferred to a convalescent home on the 14th hospital day she weighed 9 pounds 6 ounces, representing a 26 ounce weight gain during this interval (Chart 2). She was afebrile throughout her hospital stay.

DISCUSSION

The cases herein reported seem to be in keeping with the conclusions of Chung and Viscorova.[3] In spite of the persistence of diarrhea for 4 and 3 days after initiation of full strength formulas, both infants experienced steady, constant weight gains, neither dropping below the admission weight. Moreover, hydration was adequately maintained on this regime and parenteral fluids were not necessary. It is believed that parenteral fluids are a necessity when dehydration, acidosis or persistent vomiting occur; however, parenteral nutrition should be an adjunct to and should not completely replace oral nutrition.

Olac* was selected as the milk of choice because of its high protein content and because it contains a vegetable oil (corn oil) instead of animal (milk) fat. Corn oil contains more unsaturated fatty acids than animal fats, hence its greater absorbability and the production to a faster weight gain. Bananas and 5% glucose water were offered between feedings for nutrition and hydration purposes in view of Darrow's[4] contention that ". . . carbohydrates do not aggravate a diarrhea . . ."

It is conceivable that post-diarrhea feeding should be guided by the infant's weight variations and not by the number of stools, since some in-

* Olac contains 40.6 % skimmed milk solids, 31.7% Dextri-Maltose (maltose and dextrins), 17.5% corn oil, 10.1% calcium caseinate and 0.1% halibut liver oil.

fants normally continue to excrete an increased number of stools for an indefinite period of time.

It would seem that further investigation would be in order regarding the efficacy of feeding infants with diarrhea their full caloric requirements from the onset rather than the conventional method of early oral starvation.

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MECONIUM ILEUS

D. Joseph Judge, M.D. V. R. 42–8450

Intestinal obstruction in the newborn is most often caused by congenital volvulus, bands or atresia. Congenital defects such as diverticula and meconium ileus are uncommon causes of this condition. The following case is an example of the latter associated with atresia of the cecum.

CASE REPORT

A two day old infant weighing 2200 grams was admitted to the hospital with the history of absence of bowel movements since birth. The infant was a full term normally developed infant delivered by forceps extraction. The birth weight was seven pounds and ten ounces. On the day prior to admission the infant regurgitated fluid resembling bile. The temperature was 100 F. rectally. The remainder of the physical examination was normal except for distention of the abdomen. Urinalysis and hemogram were normal. A flat plate of the abdomen revealed marked distention of the colon as well as some loops of gas distending the small bowel. This had the appearance of a low complete obstruction.

An exploratory laparotomy was performed and the small bowel was dilated down to the ileum. The latter was filled with thick meconium. There was an atresia of the cecum and a portion of the large bowel. The portion of the distended bowel just above the constriction was brought out to the side of the abdominal wall and a rubber tube was placed through the mesentery to the skin surface. About ten hours later the enterostomy was opened by electric cautery. Attempts to relieve the obstruction were done by Wagensteen suction and by irrigation of the colostomy. On the day following the operation there was some regurgitation of yellow green thin fluid. Seven days after operation a small amount of fecal matter was recovered after irrigation of the colostomy. The child was treated vigorously with parenteral fluids, plasma and other supportive measures. Oral formulae feedings were taken well at first but gradually refused entirely. The infant's weight could not be maintained and with a progressive downhill course the child expired sixteen days after admission.

At autopsy the left pleural cavity contained about 20 cc. of milky yellowish fluid. The left lung was covered by a thick shaggy fibrinous exudate which was contiguous at one point to the pericardium. The lung was dark bluish red in color and appeared completely consolidated. Cut surface showed extremely variegated dark red areas alternating with paler and whitish areas. The right lung had a similar appearance but was not quite

as firm as the left. The pleural exudate on the right was less pronounced being thicker on the interlobar surfaces. Microscopic examination showed changes indicative of bronchopneumonia with the left lung completely involved in a pneumonic process. The heart was normal although the pericardium was thickened with a shaggy fibrinous exudate over the outer surface, and a smooth shiny cardiac surface. The colon was markedly reduced in its transverse diameter (0.5 cm.), throughout its length. The lumen was empty. The muscular coating and the mucosa appeared to be normal on gross inspection. The ileum was filled with a firm greenish mass to a length of 58 cm. and felt like a hard cord. At the proximal end of the obstruction the bowel was divided for the ileostomy. The small bowel above the obstruction was markedly dilated and partly filled with bright green semi-fluid material. The stomach was normal. Nowhere did the bowel show inflammatory reaction. The mesenteric vessels of the upper part of the small intestine were moderately congested. Microscopic examination of the small bowel showed slight infiltration by polymorphonuclear cells and histiocytes. The colon was normal in development. Grossly the pancreas appeared normal. Microscopic examination showed a rather marked interstitial fibrosis with reduction of the number of acini and variable dilatation of the ducts, the majority of which contained pink staining material probably representative of inspissated secretion. The islet tissue appeared to be unaffected. On one section there was an infiltration of a portion of the tissue with round cells and polymorphonuclear neutrophiles and some eosinophiles.

DISCUSSION

Rarely is the "meconium plug" not discharged in infants and a complete obstruction occurs, even with rupture of the intestine and subsequent peritonitis. The main symptom associated with the history of retained meconium is vomiting, first of water and food and later of bile stained material. Abdominal distention develops and abdominal roentgenograms will show dilated bowel loops. Although inspissated meconium is found with congenital anomalies or volvulus, the meconium in the latter instances is not as mucilaginous, greasy or putty like. The character of the meconium is related to an error in metabolism. This is due to failure of fat and protein digestion of the meconium as a result of an absence of pancreatic or biliary secretions in the intestine.

Landsteiner[1] in 1905 was the first to report the relationship between meconium and pancreatic disease. Initially Bullowa and Brennen[2] adequately described the condition in the newborn while Dodd[3], Anderson and Hild[4], and Farber[5] have all contributed excellent evaluations of the disease. Hurwitt and Arnhem[6] demonstrated that meconium ileus can

be caused by stenosis of the main pancreatic ducts. In the absence of stenosis or atresia, physical alterations of the pancreatic duct system or malformation of the entire exocrine system might occur with failure of the secretions to reach the intestine. As a result of the latter two situations atrophy of the parenchyma and finally pancreatic fibrosis occurs[7].

The common denominator regardless of the cause is pancreatic achylia. In the event that the obstruction is relieved with pancreatic extracts, the prognosis is still poor for later nutritional consequences of lack of pancreatic enzymes, fibrosis of the pancreas or failure of other secretory organs of the body occur[8]. The pathological lesion is one of interstitial pancreatitis with inflammation both interlobular and interlobular along with increased fibrosis of the organ. The pancreatic acini as well as the ducts are often dilated with the former containing inspissated secretions. The case discussed represents one with a combination of a developmental defect of the gastrointestinal tract and pancreatic disease. Although cases of meconium ileus are probably more frequent than reported and it is not uncommon for two anomalies to exist in one individual, the case seems worthy of mention.

Death when not due to the obstruction is caused by nutritional failure or intercurrent infection. Surgical intervention may be successful depending on the circumstances. However infants of the age group common to this disease cannot stand the procedures even if resection of the bowel or reduction of the obstruction is successful. The rôle of pancreatic extracts seems but a temporary palliative measure.

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THROMBOCYTOPOENIC PURPURA HEMORRHAGICA

Case Report No. 138

Robert O. Warthen, M.D. S. A. 48-3251

S. A., a white male, aged 2 years 9 months, was admitted to the Children's Hospital on April 1, 1948 because of multiple hemorrhages into the skin of 20 hours' duration. He had apparently been perfectly well until the time of admission with the exception of multiple hemorrhagic skin lesions appearing on the day prior to hospitalization. These began as small pin-point hemorrhages and progressed to large bruise-like areas within a period of several hours, occurring on the face, neck, trunk and extremities. Although many in number, the child did not appear to be clinically ill. There were no associated joint or abdominal pains nor was there any evidence of hematuria or melena.

He had been previously hospitalized at the Children's Hospital 13 days prior to this admission for an acute enterocolitis with a mildly bloody mucous diarrhea and acute pharyngitis. The diarrhea cleared rapidly on a regime of bismuth, paregoric, boiled skimmed milk, casec and sulfaguanidine (dosage of 3 gms. per day for 5 days) and he was discharged as cured after 8 days of hospitalization. On the second hospital day the mother noted several bruises on his arms and legs, these being attributed to trauma.

The child was the product of a full term uncomplicated pregnancy followed by a normal spontaneous delivery. There were no neonatal complications and he had experienced only an occasional cold since birth. Routine diphtheria, tetanus and pertussis immunizations as well as a smallpox vaccination had been completed during the first year of life.

Physical examination on admission revealed a well developed and nourished white male who did not appear acutely ill. There were numerous petechial, purpuric and ecchymotic spots dispersed over the skin of his entire body. The tongue and mucous membrane of the mouth also contained several petechiae as did the conjunctivae. The temperature was 100 F., pulse 90 and respirations 16. The tonsils were enlarged and cryptic; however, they were not inflamed. The neck was not stiff and Kernig and Brudzinski's signs were negative. The heart was not enlarged and a soft non-transmitted apical systolic murmur was faintly audible. The lungs were clear to percussion and auscultation. Examination of the abdomen revealed the liver to be palpable 3 cm. below the right costal margin and the spleen to be palpable 1 cm. below the left costal margin. The remainder of the physical examination disclosed no additional abnormalities.

Throughout the entire hospital stay the child did not appear ill with the

exception of the hemorrhagic phenomena previously noted. A few additional petechiae were noted on the day following admission; however, these did not progress to ecchymotic spots as formerly and no new petechiae occurred after that day. The spleen gradually receded to 0.5–1 cm. above the left costal margin, remaining barely palpable at the time of discharge.

Frequent blood counts were obtained disclosing a red blood cell count ranging from 4.2 to 5.9 millions, a hemoglobin varying from 12 to 18 gms. and a white blood cell count ranging from 12.0 to 20.2 thousand with a relative lymphocytosis. On the day of admission a blood platelet count of 180,000 per cu. mm., a bleeding time of 25 minutes and a coagulation time of 2.14 minutes were obtained. The thrombocyte count had dropped to 10,000 by the second hospital day and from the third through the fifth day, the blood thrombocytes were almost completely absent They began to re-appear on the sixth day when a count of 12,000 was reported. On the seventh day, a count of 50,000 was obtained, on the eighth 148,000, on the ninth 105,000 and on the tenth (day of discharge) 100,000. The bleeding time was 14 minutes 10 seconds on the third day, 6 minutes on the fourth day, 6½ minutes on the fifth day, 4½ minutes on the sixth day, 4½ minutes on the seventh day, 3½ minutes on the eighth day, and 2 minutes on the tenth day (day of discharge).

A blood culture disclosed no growth and a urinalysis was reported as negative. A sternal marrow biopsy was obtained and disclosed the various marrow elements to be present in normal proportions, megakaryocytes reduced in number and thrombocytes almost completely absent indicating an essentially normal marrow except for the diminution in megakaryocytes and thrombocytes.

Treatment consisted of 100 mgm. ascorbic acid, 15 drops of oleum percomorphum and 0.5 cc. of reticulogen (intramuscularly) daily as well as transfusions of 125 cc. of fresh whole blood on the first, third, fourth, fifth sixth and seventh days.

The temperature ranged from 90.6 to 100.4 F. (rectal) and the pulse and respirations were within normal limits throughout the hospital stay. He was discharged on the tenth hospital day after an uneventful course.

DISCUSSION

Maurice A. Selinger, M.D.: This young patient presented the picture of a somewhat typical case of acute hemorrhagic thrombocytopenic purpura which subsided spontaneously with the aid of multiple fresh whole (citrated) blood transfusions. In addition, the patient was given parenterally daily doses of reticulogen (refined liver extract with thiamine chloride, Lilly). The rôle played by these preparations is naturally open to speculation for there is certainly no evidence that they in any way act as a specific.

TABLE 1

LABORATORY DIFFERENTIAL DIAGNOSIS OF PURPURA HEMORRHAGICA IN INFANTS AND CHILDREN	BLOOD PLATELETS	BONE MARROW PLATELETS	COAGULATION TIME	BLEEDING TIME	RUMPLE LEEDE	FRAGILITY TEST	CLOT RETRACTION	PROTHROMBIN TIME	
								Quick	Howell
Non-Thrombocytopoenic Purpura (1) Hereditary telangiectasis; (2) drugs; (3) intoxications; (4) infections; (5) anaphylactoid-allergic-Schoenlein, Henoch; (6) scurvy; (7) idiopathic; (8) x-rays, radium; (9) trauma	N	N	N	↑ or N	+ or −	N	N	N	N
Thrombocytopoenic A. Primary—(1) idiopathic—Werlhof's; (2) cirrhosis of liver; (3) hypersplenism; (4) Banti's-splenic anemia; (5) congestive splenomegaly; (6) splenic vein thrombosis; (7) splenic panhematopoenia; (8) lipoid storage diseases; (9) congenital	↓	↑	N	↑	+	N	↑	N	N
B. Secondary—(1) infections; (2) intoxications; (3) drugs; (4) allergic; (5) blood dyscrasias—leukemia, aplastic anemia; (6) leukopenia; (7) x-ray, radium; (8) tuberculosis; (9) malignant neoplasms; (10) poisons	↓	N or ↓	N	↑	+	N	↑	N	N
Hemophilia	N	N	↑	N	N	↑ or N	N	N	↑
Pseudohemophilia	N	N	N	↑	+	N	↑	N	N
Megaloblastic anemia	↓	N	N	N	N	N	↑	N	N
Hemorrhagic disease of the newborn; hypoprothrombinemia; fibrinopoenia; obstructive jaundice with liver damage; avitaminosis K; congenital hemolytic icterus	N	N	↑ or N	↑ or N	+ or −	↑ or ↓	N	↑	N

Key: ↑ Prolonged. ↓ Decreased. + Positive. − Absent. N Normal.

The exciting etiologic factor is of course unknown. The above history indicates that this patient had been hospitalized about thirteen days prior to the present illness because of an acute upper respiratory infection associated or co-existing with a gastroenteritis with some blood in the stools.

In the treatment of these infections relatively small doses of sulfaquanidine were given over a period of several days. It is not possible, clinically or otherwise, to definitely implicate either the infection or sulfaquanidine in the production of the thrombocytopenic purpura. Either one could have been responsible, but there is only conjecture and there is no proof.

Throughout the course of the disease, there persisted a leucocytosis with the lymphocytic elements approaching ninety per cent. This factor suggested the possibility of an acute leukemia in spite of the absence of lymphadenopathy, but it was considered that the essentially normal bone marrow findings eliminated this diagnosis from further consideration.

The spleen was never much enlarged and this is a frequent finding in thrombocytopenia. Splenectomy was considered, but the mildness of the symptoms, their very slow progression and their early amelioration eliminated this procedure from too serious consideration.

Dr. Warthen: The diagnosis of thrombocytopenic purpura hemorrhagica is confirmed by the laboratory findings of a diminished blood thrombocyte count, prolonged bleeding and clot retraction times and a positive Rumple Leede tourniquet test. Both primary and secondary forms are recognized, the primary referring to destruction of the blood platelets after they have been formed by the marrow and the secondary denoting a suppression of the production of blood thrombocytes in the bone marrow. Examples of etiological factors involved in primary thrombocytopoenic purpura are as follows: (1) Idiopathic—Werlhof's; (2) cirrhosis of the liver; (3) hypersplenism; (4) Banti's splenic anemia; (5) congestive splenomegaly; (6) splenic vein thrombosis; (7) splenic panhematopoenia; (8) lipoid storage diseases; (9) congenital. Bone marrow platelet formation is hindered by such forms of secondary purpura as (1) infections, (2) toxic, (3) drugs, (4) allergic, (5) blood dyscrasias-leukemia, aplastic anemia, (6) leukopenia, (7) x-ray, radium, (8) tuberculosis, (9) malignant neoplasms and (10) poisons. Bone marrow platelets tend to be normal or increased in number in primary thrombocytopoenic purpura, hence splenectomy will often result in complete recovery whereas the marrow platelets in secondary purpura are generally normal or decreased in number (depending on the degree of bone marrow damage) thus accounting for the failure of splenectomy in that condition.

A complete classification of purpura hemorrhagica in infants and children with accompanying significant laboratory findings is shown in table 1.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: Edwin Vaden, M.D.
D. Joseph Judge, M.D.

By Invitation: Pearl Holly, M.D.

Edwin Vaden, M.D. G. B. 42-7237

G. B., a seven year old white female, was admitted to Children's Hospital because of weakness and frequent nose bleeds. The present illness began ten months before admission at which time the mother noticed a yellow color to the child's skin, and she complained of weakness and anorexia. A private physician was consulted and he treated the patient with medication by injection and diet for kidney trouble. After four months the jaundice began to clear up and there was some improvement in her condition.

There was no history of syphilis, tuberculosis, or of any familial diseases. The mother and father were born in Greece, but the patient and her brother were born in this country. She was the product of a nine month gestation and the delivery was uncomplicated. The vitamin and dietary intake were considered adequate and the only past illnesses were the usual childhood diseases, whooping cough, measles and mumps.

The physical examination revealed a poorly developed, undernourished female, who appeared chronically ill with a temperature of 101°F. and pulse rate of 128. The examiner stated that she was "lethargic and apparently not very intelligent." Her skin was olive colored and there was prominent cross-bun bossing of the head. There was edema of the eyelids and the eyes were lusterless; the sclerae were not jaundiced. Examination of the chest revealed the heart to be enlarged to the left and downward, and the presence of a blowing systolic murmur best heard at the apex and transmitted to the left and upward. The lungs were normal to percussion and auscultation. The abdomen was rather rotund and the spleen was greatly enlarged extending half-way between the brim of the pelvis and the costal border. The liver was palpable three finger-breadths below the right costal margin. The hands were described as spade-like with short, stubby fingers. Neurological examination was negative.

On admission there were 3,000,000 erythrocytes with 3.5 gms. of hemoglobin. The blood smear showed numerous microcytes, many macrocytes, marked achromia, some poikilocytosis and basophilia, and some normoblasts. There were 12,000 leucocytes with 83 per cent neutrophiles (78 per cent segmented, 4 per cent staffs, 1 per cent metamyelocytes), 1 per cent eosinophiles and 10 per cent lymphocytes and 6 per cent small mononu-

clear cells of the lymphocytic series. The thrombocyte count was 175,000. X-rays of the skull, thorax and long bones were taken. The examination of the chest revealed an increased porosity of the ribs and bony thorax. The heart was slightly enlarged and the lung fields were clear. The x-rays of the skull and of the long bones are seen in Figure 2.

Four months before admission the patient had laboratory studies on the outside at which time the serology was negative, a sickling test was negative; the qualitative Van den Bergh gave an indirect reaction with 5.5 mgm. of bilirubin by the quantitative method. A fragility test was done and hemolysis began in a 0.35 per cent salt solution (0.38 to 0.44 per cent normal) and was complete in 0.20 per cent solution (0.32 to 0.34 per cent normal). A routine urinalysis was normal and negative for bile.

The patient had two other admissions to the hospital in the next nine months. On her second admission she had three whole blood transfusions and was discharged on the third day. On the third admission the patient was in very poor condition with 4.3 gms. of hemoglobin and 1,960,000 erythrocytes and had a high fever. She received a transfusion, but failed to improve and expired 16 hours after admission. Necropsy permission was refused.

DISCUSSION

Pearl B. Holly, M.D.: The patient was a seven year old white female, born in this country of Greek parentage. She entered the hospital with very little history preceding her present illness 10 months ago, though I would suspect that she probably did have organic changes since infancy. Her prominent cranial bossing, short spade-like fingers, hepatomegaly and splenomegaly and olive-tinted skin may have been overlooked in preceding examinations. The bony changes apparent in the x-ray films did not appear in 10 months. In addition to these clinical findings, we see in the blood picture a marked microcytic hypochromic anemia with a 3,000,000 red-count and only 3.5 gms. of hemoglobin. The only condition where we find this marked microcytic hypochromic anemia in association with splenomegaly and hepatomegaly, without a history of blood loss, without a history of insufficient iron intake, without a history of numerous infections interfering with iron absorption and utilization and probably in the course of her illness, without a response to iron therapy, is a disease known as Cooley's anemia or Mediterranean anemia or target cell anemia or thalassemia major or familial microcytic hypochromic anemia. This is the only type of microcytic hypochromic anemia that does not respond to iron. This disease occurs in families and is inherited as a recessive characteristic. The blood findings on the children and parents in this family would be of great interest here. I would expect to find a mild microcytic hypochromic anemia in one of the parents or grandparents.

When Cooley first described this anemia, he emphasized its occurrence in infants and very young children. His patients had mongoloid facies, a protruding large abdomen with a large liver and large spleen, an anemia with normoblasts in the peripheral blood stream and no response to any known therapy. These individuals usually died in infancy or very early childhood. In addition to their anemia, jaundice was commonly apparent though mild, compared to the amount of anemia present. This is in contrast to congenital hemolytic anemia where the jaundice is directly proportional to the amount of blood cells destroyed. The anemia is not therefore an anemia due to destroyed cells only but is probably also due to a lack of or interference with the normal formation of the red blood cells.

In the past 10 years we have been recognizing that these patients may survive to the age of six, eight and even fourteen years of life. A milder form of this disease compatible with long life has been described in adults (called thalassemia minor) in whose families thalassemia major has been discovered in infants. It is quite interesting in the adult in that we find a microcytic hypochromic form of anemia with a low hemoglobin value and a normal red cell count (i.e. 5–6 million red blood cells and 10 gms. of hemoglobin). Target cells are present, the spleen may be enlarged and a mild degree of jaundice may be apparent. The adult gets along very well with this mild anemia and lives a comparatively normal life. These adult cases were first described by Wintrobe in Baltimore 1931, Dameshek in Boston 1931, Doan and Strauss, and Valentine and Neils. All cases were among people of Mediterranean descent and most of the adults had low grade anemia, splenomegaly and lack of response to iron therapy. Valentine and Neils studied the Italian population in Rochester, N. Y. where they found that 10–20 per cent of the Italian population in their region had some form of this anemia among the adults; and in those families they were able to elicit a good history of/or to find cases of true Cooley's anemia among the infants.

It is a very interesting disease in that we probably have here a congenital anomaly or malformation of the individual red blood cells. These individuals have enough iron in their body. On post-mortem examination, iron deposits are scattered throughout the reticulo-endothelial system. They have, as far as we know, adequate intake of all the necessary materials, i.e., proteins, vitamins and minerals, etc., to make red blood cells. There is no gross blood loss. Yet the hemoglobin formation is mildly to markedly deficient and our present modes of therapy have no effect on the latter.

In summary, the laboratory findings are characteristically a microcytic hypochromic anemia, many target cells, mild to moderately increased ic-

terus index and a decreased osmotic fragility test due to the presence of target cells. All these findings were present in this patient.

The x-ray plates showed characteristic changes in skull and long bones found in chronic hemolytic anemias that occur and persist through early childhood—the hair-on-end appearance in the skull bones, the widened squared ends of the long bones and widening of the medulla (hyperplastic marrow), with thinning of the cortex.

FIG. 1. G. B. Characteristic mongoloid facies of Mediterranean anemia

In conclusion, we have here a patient with thalassemia major, age 7 years, showing the characteristic clinical, laboratory and x-ray changes seen in this disease.

PATHOLOGICAL DISCUSSION

E. Clarence Rice, M.D.: The diagnosis of Mediterranean anemia or thalassemia major is correct. The fact that the patient is of Italian origin and has marked hemolytic anemia with the presence of nucleated red blood cells would certainly suggest the diagnosis.

In the practice of pediatrics the pediatrician more often encounters a triad of somewhat similar anemias than does the physician seeing adult patients. These anemias associated with jaundice are as follows: Mediterranean anemia, congenital hemolytic anemia and sickle cell anemia.

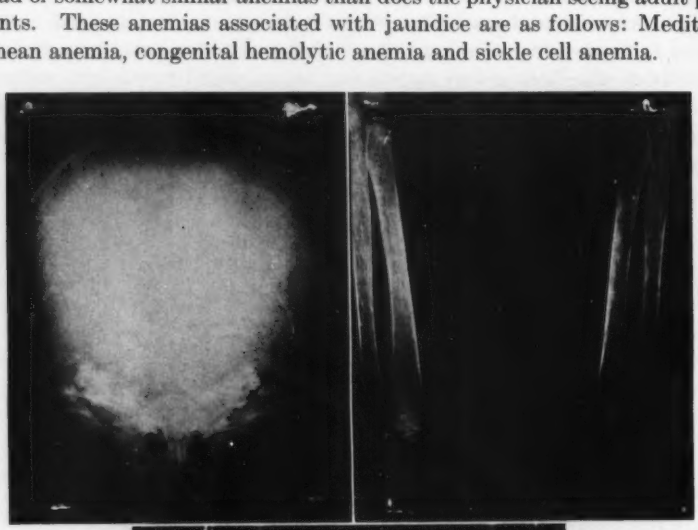

FIG. 2. G. B. X-rays of the long bones, forearms, wrists, hands and skull showing the characteristic medullary changes with a widening of the metaphyses, hair-on end appearance to the skull and the dilated trabeculae in the medullary regions.

It is interesting to note that heredity plays a part in each, the latter being usually associated with members of the negro race, congenital hemolytic anemia being due to a dominant defect which is transmitted and Mediterranean anemia showing evidence of a familial and racial background.

All of these anemias are hemolytic in type and may show a variety of the

members of the erythrocytic and leucocytic series. In the past they have at times been mistaken for leukemia and have been associated with the designation, von Jaksch's anemia. The peculiar sickle shape of the erythrocytes in a negro, the erythroblastic anemia in one of Mediterranean stock and the presence of a normocytic hypochromic anemia with usually increased fragility in a patient with a familial anemia should be sufficient to suggest the probable diagnosis in these three diseases.

Rarely does the adult patient present the findings of thalassemia or sickle cell anemia and the statement has been made that patients with Mediterranean anemia do not live to adult life; however, we know of a patient who is now over 40 years of age who was reported during childhood along with two siblings as a case of congenital Banti's disease. We have seen the disease recognized within a few months after birth. There is no reason why any of these cannot manifest themselves during infancy.

The following hemolytic anemias of children have all been recognized as entities in recent times due to modern diagnostic aids and immunological investigations; erythroblastosis fetalis, sickle cell anemia, congenital hemolytic anemia and Mediterranean anemia.

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*Sherman, H. C.: Some Recent Advances in the Chemistry of Nutrition, J.A.M.A. 97: 1425–1430 (Nov. 14) 1931.